S_NAr Based Macrocyclization *via* Biaryl Ether Formation: Application in Natural Product Synthesis

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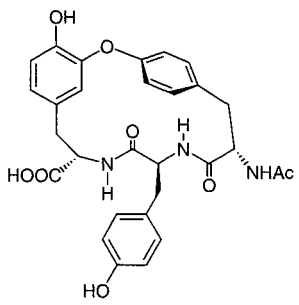
ABSTRACT: A new macrocyclization method based on intramolecular S_NAr reaction developed recently in this laboratory has been summarized. Mild conditions, high yield and versatility are the characteristic features of the present method. Application to the synthesis of 14-, 16- and 17-membered macrocycles found in natural products has been demonstrated.

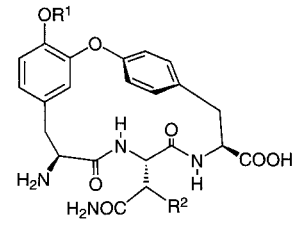
I. Introduction

An array of macrocycles containing a biaryl ether bridge exists in nature. These compounds range from the monocyclic: K-13 (**1**),[1] OF4949 I-IV (**2**),[2] to the bicyclic: piperazinomycin (**3**, RA I-XIV),[3] bouvardin (**4**)[4] (Figure 1) and to the exceedingly structurally complex polycyclic glycopeptide antibiotics examplified by vancomycin (**5**),[5] and teicoplanin (**6**)[6] (Figure 2). Most of these molecules have significant biological activities. For example, vancomycin is a drug of choice as well as a drug of last resort for the treatment of infections due to methicillin-resistant *staphylococcus aureus* and other gram-positive microor-



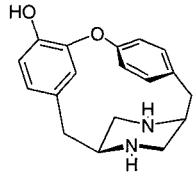
K 13

1

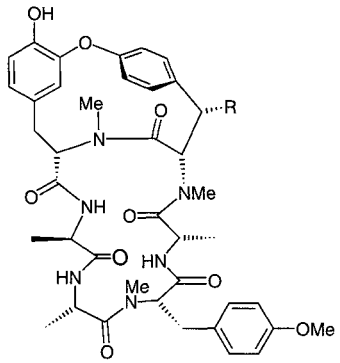


OF4949-I, R^1 = Me, R^2 = OH
OF4949-II, R^1 = H, R^2 = OH
OF4949-III, R^1 = Me, R^2 = H
OF4949-IV, R^1 = H, R^2 = H

2

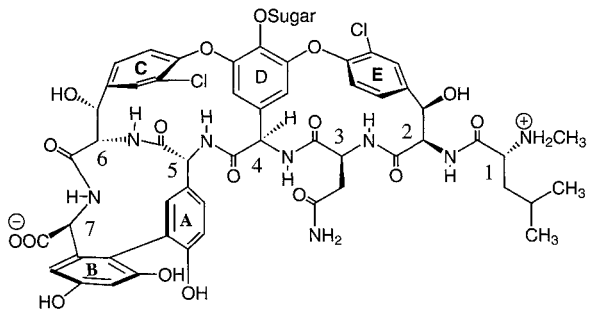


3 piperazinomycin

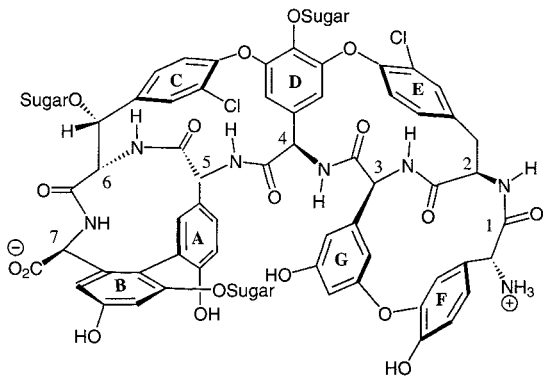


4a bouvardin R = OH
4b deoxybouvardin R = H

Figure 1



vancomycin **5**



teicoplanin **6**

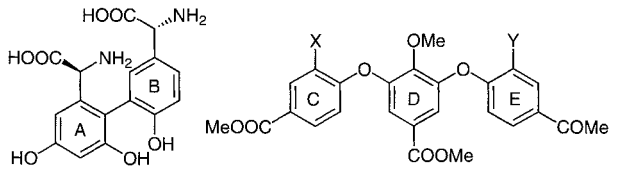
Figure 2

ganisms. As an important antibiotic, it has spurred multidisciplinary interest over the last 35 years.[7]

The architectural complexity and biological activity of these compounds have attracted much attention and have provided synthetic chemists with the impetus for the development of new synthetic reactions.[8] The configurational lability of the amino acids, especially the aryl glycines found in the polypeptidic macrocycles have provided yet another prospect for organic chemists, as one might realize the difficult synthetic endeavour under extremely mild conditions.

While many bond disconnections could be considered for the synthesis of the above mentioned compounds, mainly two strategies are evident from the view point of rational retrosynthetic analysis. The first one consists of formation of the functionalized biaryl ether followed by macrolactamization which has been successfully implemented in the total synthesis of K-13 (**1**) and OF 4949 I-IV (**2**).[8] For construction of the biaryl ether bond, classic Ullmann ether synthesis was employed in most cases. However, the incompatibility of amino acid functionalities with the harsh Ullmann conditions has hampered the direct coupling of two tyrosine units. Consequently, the biaryl ether bond had to be formed before the construction of the amino acid side chains. Being linear, this synthetic sequence has the advantage that the macrolactamization techniques are well-documented. Nevertheless, this strategy has met with very little success in the vancomycin field.

The second strategy involves the preparation of a linear peptide followed by biaryl ether formation as the key cyclization step. The main attribute of this strategy is its convergency. However, the existing methods for this crucial bond forming process are scarce, especially when mild conditions are mandatory because of the sensitive functionalities present in the natural products. Towards this end, an elegant thallium trinitrate (TTN) promoted phenolic oxidative coupling reaction has been developed by Yamamura *et al*[9] and illustrated in their biomimetic total syntheses of K-13 (**1**),[9a] piperazinomycin (**3**)[9b], deoxybouvardin (**4**)[9c] and vancomycin model.[9d] This method, modified later by Evans *et.al*,[10] has been applied in their brilliant synthesis of the hitherto most advanced bicyclic vancomycin model. Alternatively, on modifing the classic reaction conditions and choosing judiciously the reaction partners, Boger *et.al*[11] have disclosed a macrocyclization procedure based upon the intramolecular Ullmann reaction. The methodology has been successfully applied in their total synthesis of piperazinomycin,[11a] bouvardin[11b] and simple vancomycin models.[11c] However, the presence of the very racemization prone arylglycines in vancomycin may hamper further application of Ullmann based strategy which, even under improved conditions, still requires heating in pyridine at 110°C in the presence of strong bases.

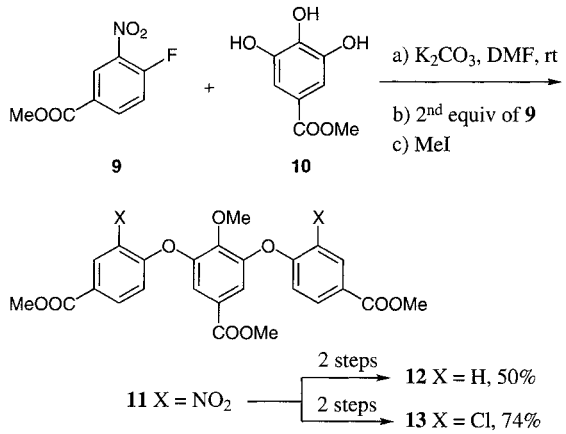


Actinoidic acid **7**

8a X = Y = Cl, from vancomycin and teicoplanin
8b X = Y = H, from ristocetin and A35512B
8c X = H, Y = Cl, from avoparcin and actaplanin

Figure 3

We have started our work in the vancomycin field at the begining of 1993 and our first target was the synthesis of two degradation products: actinoidic acid (**7**) and triaryl diethers (**8**) (Figure 3). Meyer's oxazolidine chemistry was employed in our synthesis of compound 7,[12] while an aromatic nucleophilic substitution[13] (S_NAr) was the key step in our synthesis of triaryl diethers (**8**)[14] (Scheme 1).



Scheme 1

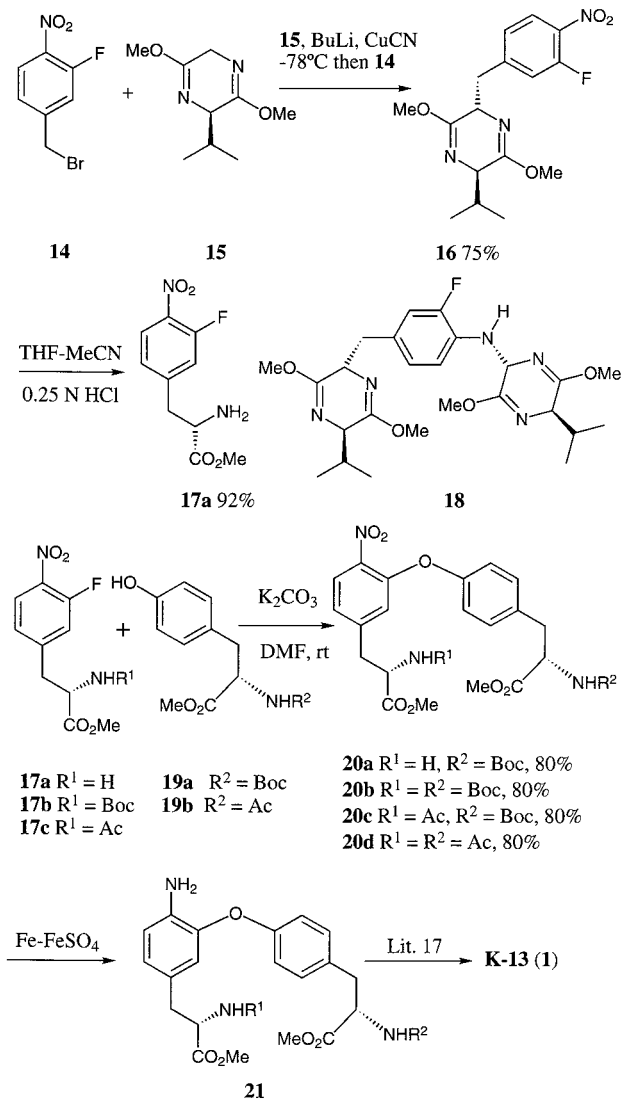
Methyl 3-nitro-4-fluorobenzoate (**9**) and methyl gallate (**10**) were selected as reaction partners. Compound **9** was structurally designed as to carry a nitro function, not only serving together with the ester group to promote the S_NAr reaction, but also to provide an access to the substitution pattern (Cl, H) on position *ortho* to the aryl ether linkage. Sequential addition of 2 equiv. of **9** at room temperature into a solution of **10** gave, after *in situ* methylation, the desired triaryl diethers **11** (88%) in a one-pot fashion. The observed regioselectivity may be explained by the conjugating effect of the ester function which might enhance the kinetic acidity of the 4-hydroxy group related to that of the two lateral hydroxy groups. As a consequence, the conjugate base of the 3- and 5-hydroxy groups should be more nucleophilic leading to the 3- and 5-O-arylated compound under thermodynamically controlled conditions. The two step transformation of **11** to **12** and **13** is straightforward *via* common diazonium intermediate.

At this point, we thought that the mild S_NAr conditions might well be amenable to the synthesis of more complex biaryl ether compounds containing sensitive functional groups. The idea was illustrated in the formal total synthesis of K-13 (Scheme 2).[15]

The unknown L-(*S*)-3-fluoro-4-nitrophenylalanine derivatives **17a-c** were prepared by alkylation of Schöllkopf's bislactim ether[16] with 3-fluoro-4-nitrobenzylbromide followed by hydrolysis and standard protection procedures. The reaction of 3-fluoro-4-nitrobenzyl bromide (**14**) with the lithium azaenolate of **15** gave only a poor yield (<10%) of alkylated product **16**, presumably due to the high acidity of benzylic protons and more importantly, to the presence of multi-electrophilic centres in **14**. However, when the lithium salt of **15** was transmetalated into a

Biographical Sketch

Jieping Zhu was born in 1965 in Zhejiang, P. R. China. He received his B.Sc. degree from Hanzhou normal college in 1984 and M.Sc. degree from Lanzhou university in 1987 under the supervision of Professor Y.-L. Li. In 1988, he moved to France and obtained his Ph.D. degree in 1991 from Université Paris XI under the supervision of Professor H.-P. Husson. After a one and half year post-doctoral stay with Professor D. H. R. Barton at Texas A & M University in USA, he joined Institut de Chimie des Substances Naturelles, CNRS as a "*Chargé de Recherche*" in Dr. Beugelmans' group.



Scheme 2

higher order (H.O.) organocuprate, **16** could be reproducibly isolated in 75% yield, provided that the reaction was run at -78°C. That S_N2 (displacement of bromide) prevails over S_NAr (displacement of fluoride) under these conditions may be explained by the HSAB principle considering the organocuprate as a soft nucleophile. Hydrolysis of **16** under acidic conditions afforded the desired amino ester **17a** in 92% yield. A significant amount of disubstituted compound **18** was formed when the reaction of **14** with H.O. organocuprate of bislactim ether **15** was run at -20°C. Coupling of **17** with protected L-tyrosine (**19**) gave smoothly the diastereomerically pure isodityrosine derivative (**20**) in high yield. Reduction of nitro group (Fe-$FeSO_4$) gave the amino compound **21** which had already been converted into K-13 (**1**) by Rama Rao *et.al*.[17] The preparation of compound **20** constitutes the first example of one-step synthesis of chiral bis-aminoacid biaryl ethers. In their first synthesis of 16-membered vancomycin model, Hamilton *et al*.[18] have also employed such intermolecular S_NAr reaction using a dinitro activated substrate for constructing the biaryl ether bond.

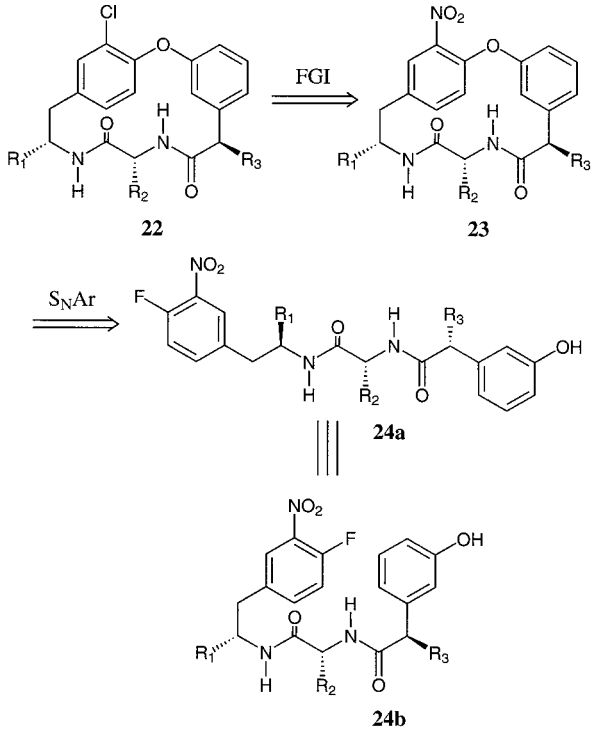
Encouraged by these results and knowing that the macrolactamization to 16-membered **C-O-D** and **D-O-E** rings of vancomycin was inefficient,[19] we became interested in developing a new ring closure method *via* intramolecular S_NAr reaction for the crucial biaryl ether bond formation. The successful implementation of this strategy and its application in natural product synthesis is the main topic of the present account. In a recent article, Rama Rao *et.al*.[8] have reviewed all synthetic methods developed in recent 10 years including the intramolecular SNAr methodology towards the synthesis of vancomycin and related cyclic peptides. However, the design conception and a large part of synthetic works presented in this account do not overlap with Rama Rao's excellent review.

II. Synthesis of 16-membered macrocycles *via* intramolecular S_NAr reaction

II-A. Development of strategy

In designing a new macrocyclization method, we sought to address the following issues: 1) increasing the yield of cyclization product; 2) avoiding the harsh reaction conditions, a requirement of paramount importance in light of the sensitive functionalities present in natural products; 3) introducing a single substituent *ortho* to the biaryl ether linkage; 4) enhancing the versatility (flexibility) of the cyclization procedure and 5) controlling the atropdiastereoselectivity in the ring closure process. The last point deserves some comments. In vancomycin family glycopeptides, the rotation of biaryl ether bond through the 16-membered macrocycles (**C-O-D-O-E** ring) is restricted. Accordingly, the presence of a single chlorine substituent on each aromatic ring creates potentially four atropdiastereoisomers and therefore the selective formation of the correct atropisomer found in vancomycin presents a formidable challenge. Although the biomimetic approach developed by Yamamura[9d] and Evans[10] for constructing the monocyclic **C-O-D**, **D-O-E** and bicyclic **C-O-D-O-E** moieties represented a remarkable progress towards the total synthesis of this class of natural products, the presence of two chlorine atoms on rings **C** and **E** was unavoidable *via* thallium trinitrate mediated coupling. Subsequent removal of one chlorine atom from each ring in a diastereoselective fashion would be uncertain.

To fulfill the above mentioned requirements, we thought that an intramolecular S_NAr reaction[13] could be a good candidate. As one of the most important reactions for regioselective nucleophilic aromatic substitution, the classic S_NAr reaction has attracted a great deal of mechanistic studies and has been applied to C-C as well as to C-heteroatom bond formation. However, to the best of our knowledge, there was, at the outset of our work, no report dealing with its application in macrocyclization though the formation of 5-, 6- and 7-membered ring compounds was documented.[20] The retro-synthetic analysis of a 16-membered model **C-O-D** ring of vancomycin based on this idea is shown in Scheme 3.



Scheme 3

Cyclization is usually disfavored because of loss of entropy and gain of strain associated with the ring formation. For a given cyclization, the rate of intramolecular reaction of a bifunctional chain molecule depends in a very marked way on conformational preference of the substrate. The linear tripeptide **24**, a precursor for our macrocyclization studies, may exist in two distinct conformations: a β-pleated sheet **24a** and a turn structure **24b** (bent conformation). Several distinct structural factors of **24** may favor the latter and thus favor the desired cyclization: 1) π-π interactions[21] between an electron-deficient fluoro-nitro substituted aromatic ring and an electron-rich phenoxide ring (electron donor-acceptor (EDA) or charge transfer (CT) model) or an attractive electrostatic interaction arising from positively and negatively charged atoms (the atomic charge model); 2) intramolecular hydrogen bonds;[22] 3) presence of glycine or D-amino acids in the peptide chain which could favor bent conformations over β-pleated sheets.[23] If the pre-arranged conformation was really necessary for such macrocyclization (proximity effects), then this last point should not be determinant for the conformational preferences as shown in our successful synthesis of K-13 (**1**) (*vide infra*) where the peptide chain only comprised L-(*S*)-amino acids.

To gain information regarding the solution conformations of the linear cyclization precursor, we have carried out a computational simulation (macromodel, Batchmin Version 3.5a, Oplsa force field,[24] water set). Figure 4 shows the lowest energy conformation observed for **24** (R_1=R_2=R_3=H). As expected, a conformer where a parallel face-to-face π stacked geometry between two aromatic rings is the one that has the lowest energy. The two reactive sites (HO and C_F) in this conformation were thus placed within 4.283 Å, a distance which should result in low activation energy and favorable entropy for cyclization.

The realization of this strategy is shown in Scheme 4.[25] Commercially available 4-fluorobenzaldehyde (**25**) was nitrated to give quantitative yield of 4-fluoro-3-nitrobenzaldehyde (**26**), which was then transformed into 4-fluoro-3-nitrobenzylnitrile (**27**) by sequential reduction, bromination and cyanation. Chemoselective reduction of the nitrile function

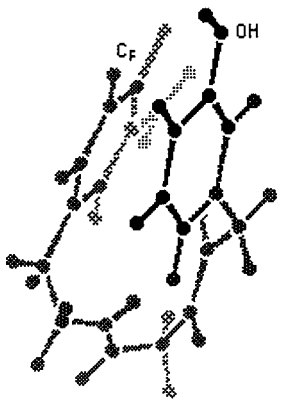
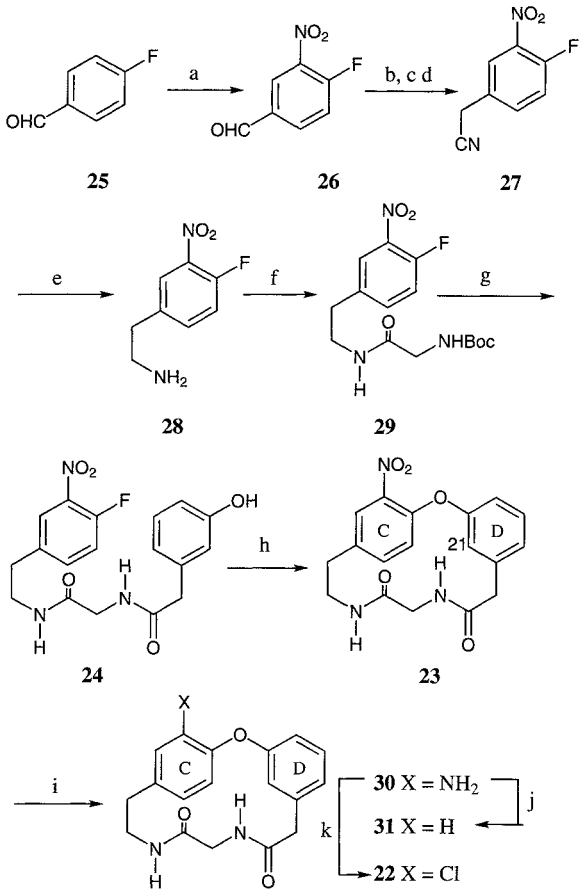


Figure 4

afforded the crude amine **28** which was coupled directly with N-Boc glycine to afford the amide **29** (87%). Mild acid deprotection of **29** followed by amide bond formation with 3-hydroxyphenylacetic acid provided **24** (94%) without any complication due to free hydroxy group.

Treatment of a DMF solution of **24** with 4 equiv. of anhydrous potassium carbonate at room temperature for 6 hrs afforded a single compound in 95% isolated yield. Macrocyclization was first run at 0.004 M concentration, but we quickly realized that the high dilution technique was, in fact, not necessary and that macrocyclization could be efficiently carried out at 0.01M concentration. Spectral data (^{1}H and ^{13}C NMR, IR and elemental analysis) of the product were consistent with the macrocyclic structure **23**. A characteristic feature of this cyclized product in ^{1}H NMR spectra is the upfield shifted H-21 signal due to the anisotropic effect of aromatic C ring π-cloud.

The potential of this approach was demonstrated by converting the macrocyclic compound **23** into the model **C-O-D** ring **31** and **22**. Thus,



Reagents: a) HNO_3-H_2SO_4; b) $NaBH_4$; c) PBr_3; d) Et_4NCN; e) AlH_3 or $NaBH_4$, TFA; f) DCC, Et_3N, N-Boc glycine; g) TFA, then Et_3N, DCC, m-hydroxyphenylacetic acid; h) K_2CO_3, DMF; i) Fe-$FeSO_4$; j) ^{t}BuONO, DMF;(k) $NaNO_2$, HCl, CuCl-$CuCl_2$.

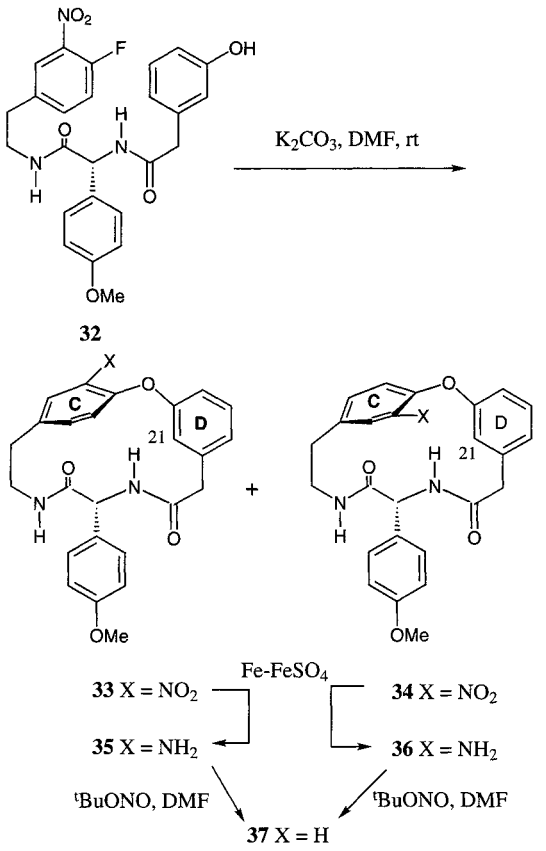
Scheme 4

reduction of the nitro compound **23** (Fe-$FeSO_4$) provided the corresponding amine **30** in excellent yield. Direct reductive deamination of **30** under Doyle's conditions gave **31** (66%). Conversion of **30** into **22** was not as straightforward as expected. After repeated trials, the best results were obtained when the Sandmeyer reaction was performed in the presence of both reductant (CuCl) and ligand transfer agent ($CuCl_2$). The successful preparation of **22** represents the first example where a single chlorine atom was correctly incorporated into the aromatic **C** ring.[26]

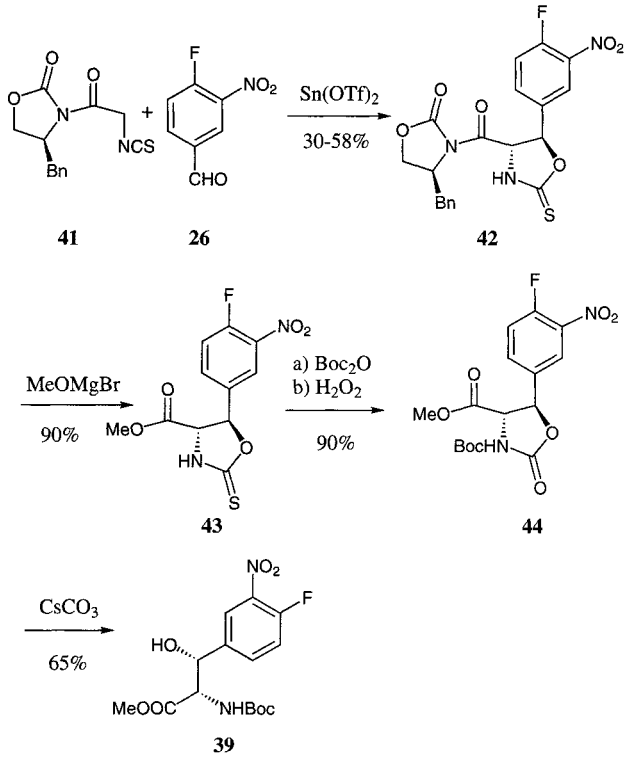
Having established the validity of our approach, we turned our attention to the preparation of the more elaborated **C-O-D** ring[27] (Scheme 5). Tripeptide **32** incorporating a racemization prone para-methoxyphenyl glycine was synthesized as described before. Interestingly, macrocylization under the previously established conditions (4 equiv. K_2CO_3, 0.01M in DMF) afforded two separable atropisomers **33** and **34** (54/40) in 94% yield.

The structure and stereochemistry of **33** and **34** were determined from extensive NMR studies (COSY and NOESY). A control experiment showed that there was no interchange of **33** and **34** under the standard S_NAr reaction conditions, thus confirming that both are kinetic products. Thermal atropisomerization of **33** and **34** was carried out in DMSO-d_6 and a partial equilibrium was observed only after prolonged heating over 110°C.

The definitive structural proof relied upon chemical transformation. Reduction (Fe-$FeSO_4$) of each atropisomer **33** and **34** gave **35** and **36** in yields of 54% and 80% respectively. Reductive deamination of either **35** or **36** afforded the same compound **37** {[α]D -30, c 0.5, DMF}.



Scheme 5



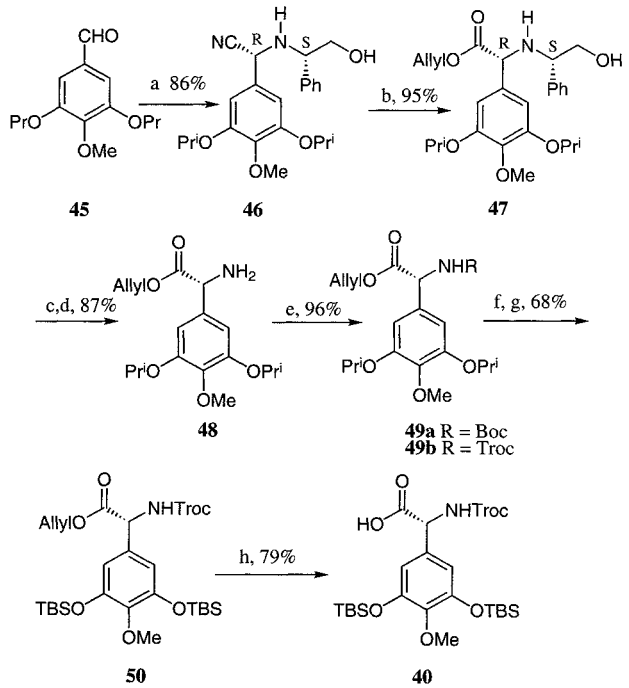
Scheme 6

II-B. Synthesis of fully functionalized 16-membered C-O-D ring of vancomycin

This novel macrocyclization method was subsequently applied to the synthesis of the fully functionalized C-O-D ring of vancomycin **38**.[28] To achieve the desired macrocyclization precursor, two non-natural amino acids **39** and **40** were needed. The β-hydroxyl α-amino acid: (2*S*,3*R*)-β-(4-fluoro-3-nitro) phenylserine (**39**) was synthesized as shown in Scheme 6. Aldol condensation[29] between isothiocyanate (**41**) and 4-fluoro-3-nitrobenzaldehyde (**26**) [$Sn(OTf)_2$, N-ethyl piperidine] afforded *syn* aldol, isolated as the internally derivatized heterocycle **42** in moderate chemical yield and *syn/anti* selectivity. Other metal enolates such as Li, B, and Ti have also been tried for the key aldol process, however, none of them gave satisfactory yield. We think that the presence of fluoro and nitro functions in the aromatic ring may have some deleterious effect, at least on the facial selectivity. Treatment of **42** with magnesium methoxide in methanol gave the corresponding methyl ester which was transformed into oxazolidinone **44** in a two step sequence. Hydrolysis of **44** carried out under different conditions was found to be problematic due to the competitive attack of the nucleophile onto the *endo* and *exo* carbamate functions. The best result was obtained with $CsCO_3$ in MeOH which led to the desired compound **39** in 65% yield. The corresponding didehydroamino ester was inevitablely produced in 10 to 20% yield.

D-(*R*)-N-Troc-3,5-bis*t*butyldimethylsilyloxy-4-methoxy phenyl glycine (**40**) was first prepared *via* asymmetric Strecker synthesis[30] as key step (Scheme 7). 4-Methoxy-3,5-diisopropyloxy benzaldehyde (**45**) was prepared in 6 steps from methyl gallate (**10**) without column chromatography purification (62% overall yield).[28] Treatment of **45** with (*S*)-phenylglycinol in CH_2Cl_2 at rt for 1 h followed by sequential addition of MeOH and TMSCN at 0°C afforded a mixture of two readily separable diastereoisomers from which the desired one **46** was isolated (86%) and transformed into α-amino allyl ester **47** (95%) using gaseous HCl saturated allyl alcohol. Oxidative cleavage of the chiral auxiliary with $Pb(OAc)_4$, and protection of the resulting primary amine afforded compound **49** (84%) which was converted into TBS ether **50** without event. Deprotection of allyl ester was realized under our recently developed conditions[31] [$Pd(PPh_3)_4$, $NaBH_4$, THF] to provide the desired aminoacid **40** (79%) whose optical purity (*ee* 80%) was determined by conversion to the corresponding (*S*)-α-methyl benzylamide.

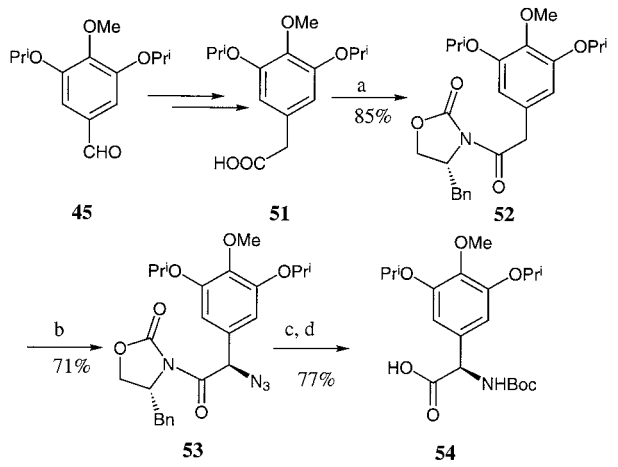
Compound **40** was used without further purification in terms of enantiomeric purity for the synthesis of macrocycle **38**, we have nevertheless developed a more enantioselective synthesis of **54** (Scheme 8). One-carbon homologation of the aldehyde **45** under classic conditions afforded



Reagents and Conditions: a) (*S*)-phenylglycinol, CH_2Cl_2, TMSCN; b) CH_2=$CHCH_2OH$ HCl; c) $Pb(OAc)_4$, CH_2Cl_2-MeOH; d) 2N HCl; e) Boc_2O, or TrocCl, $NaHCO_3$, H_2O-CH_2Cl_2; f) BCl_3; g) TBSOTf, 2,6-lutidine; h) $Pd(PPh_3)_4$, $NaBH_4$, THF.

Scheme 7

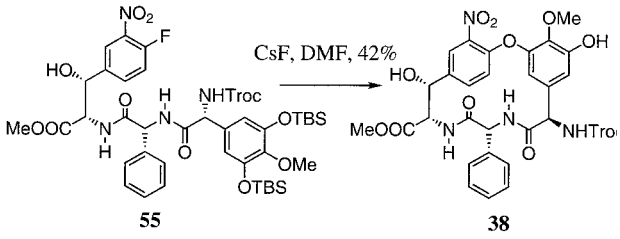
the acid **51** which was transformed into the imide **52**. Electrophilic azidation under Evans' conditions[32] gave the diastereomerically pure azide **53** in 71% isolated yield. Hydrogenation of **53** in the presence of Boc_2O followed by hydrolysis yielded enantiomerically pure D-(*R*)-N-Boc-3,5-diisopropyloxy-4-methoxy phenyl glycine (**54**) in excellent yield.



Reagents and conditions: a) Me_3CCOCl, Et_3N, THF, then lithium salt of (*R*)-4-phenylmethyl-2-oxazolidinone; b) KHDMS, $TrisylN_3$, THF, then Me_2CO, NaI, NaOAc; c) 10% Pd/C, Boc_2O, EtOAc; d) LiOH, THF-H_2O.

Scheme 8

Assemblage of amino acids **39**, **40** and D-(*R*)-phenylglycine under standard conditions (EDC, HOBt) led to the linear tripeptide **55**. Less than 5% racemization occurred under these conditions and the diastereomerically pure compound was obtained by flash chromatography. Treatment of **55** with anhydrous CsF in DMF (0.01 M) allowed deprotection of silyl ether and intramolecular S_NAr reaction to be performed in a one-pot fashion yielding the macrocycle **38** as a mixture of two atropisomers in 42% non-optimized yield (Scheme 9).



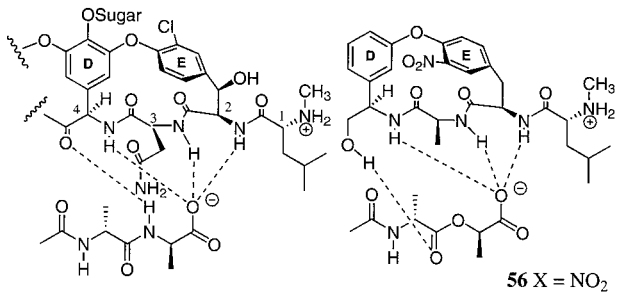
Scheme 9

II-C. Design and synthesis of a modified vancomycin binding pocket

The recent emergence of vancomycin resistance has been met with great apprehension and the modification of the vancomycin target has been proposed as the principal mechanism of resistance.[7] Sensitive bacteria synthesize cell wall peptidoglycan (PG) strands terminating in D-Ala-Ala while resistant bacteria are able to synthesize D-Ala-D-Lactate. *In vitro* binding studies have shown that the affinity of vancomycin for N-Ac-D-Ala-D-Lactate is 1000 times less than its affinity for N-Ac-D-Ala-D-Ala, paralleling the 1000-fold reduced sensitivity of vancomycin-resistant bacteria to drug.

In the context of searching for synthetic analogues which may have enhanced affinity towards the D-Ala-D-Lactate, we have designed a modified carboxyl binding pocket of vancomycin. We conceived that compound **56** could, *a priori*, display increased affinity towards N-Ac-D-Ala-D-lactate mediated by the primary hydroxy group. This polar function could be considered as an hydrogen donor which, if the solution conformation permitted, could form an hydrogen-bond with the ester function (hydrogen acceptor) of D-Ala-D-lactate, thus restoring the four hydrogen-bonds required for inhibiting the cell wall biosynthesis of modified peptidoglycan (Figure 5).

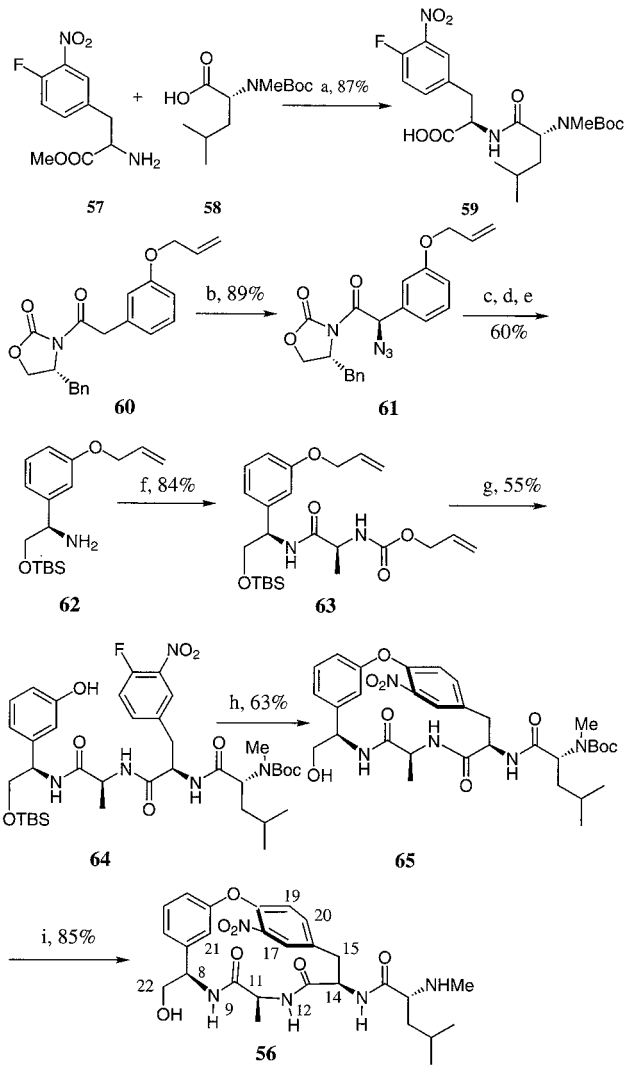
Synthesis of **56** is shown in Scheme 10.[33] Dipeptides **59** and **63** were prepared uneventfully. Simultaneous reductive deprotection of O-allyl and N-alloc groups of **63** using the reagent combination $LiBH_4$-$Pd(PPh_3)_4$[31] furnished the corresponding aminoalcohol which was coupled directly with the dipeptide **59** to give the tetrapeptide **64**. In order to avoid epimerization, using DPPA as coupling reagent is mandatory for this 2+2 coupling reaction.



Vancomycin-D-Ala-D-Ala complex (**56**)-D-Ala-D-lact complex

Figure 5

Macrocyclization of **64** proceeded smoothly (anhydrous CsF in dry DMF, 0.01M, rt) to afford the 16-membered macrocycle **65** (63%) as a



Reagents and conditions: a) (i) EDC; (ii) K_2CO_3, H_2O; b) KHMDS, Trisyl N_3 then AcOH; c) $LiBH_4$, Et_2O; d) $SnCl_2$, MeOH; e) TBDMSCl, DMAP, Et_3N; f) N-Alloc-(L)-Alanine, EDC; g) i) $Pd(PPh_3)_4$-$LiBH_4$ ii) DPPA, **59**, DMF, Et_3N; h) CsF, DMF; i) HCl-CH_3CN.

Scheme 10

single isolable atropisomer. Removal of Boc protective group (0.1N HCl in CH_3CN) gave the desired product **56** in 85% yield. The configuration of newly formed chiral axe was determined from the detailed NMR analysis of final compound **3**. Characteristic and diagnostic of P configuration (Helix nomenclature) of the chiral axe, an intense NOE was observed between H-20 and H-15', H-21 and more importantly H-14. Similarly, no NOE was observed between H-17 and H-14 which could indicate a M configuration of chiral axe. Significantly, NH-12 shows NOE to the NH-9. These observations established that NH-12 is on the front face of the structure and that three amide protons point in the same direction instead of a normal up/down/up conformation in the β-pleated sheet form. This indicated that the carboxylate anion binding pocket is present as a major conformation of **56** in the absence of N-Ac-D-Ala-D-Ala, in sharp contrast to vancomycin where such conformer was formed only in the presence of cell wall peptide.

The binding properties of **56** with Ac-D-Lact were studied by ^1H NMR titration experiment and curve fitting method. A dissociation constant (K_d) of 5 x 10^{-4} between **56** and Ac-D-Lact has been determined. About 83% of **56** was present in the bound form when 1.05 equiv. of AcLAct was added.[34] This value is higher than that of the binding between vancomycin and Ac-D-Ala where only 69%[35] of antibiotic was in the complex form at the highest concentration of Ac-D-Ala.

III. Synthesis of 14-membered macrocycles *via* intramolecular S_NAr reaction

To study the generality of the S_NAr based macrocyclization methodology, we subsequently extended it to the synthesis of 14-membered macrocycles found in natural products. In the course of this study, we addressed the following two issues: 1) Does chloride could serve as leaving group in intramolecular S_NAr reaction? 2) Does nitro group located *para*, instead of *ortho*, to the leaving group could activate the nucleophilic addition?

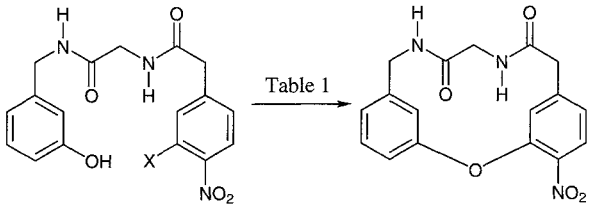
III-A Synthesis of model F-O-G ring of teicoplanin

When the linear tripeptide **66a** prepared in the usual manner was submitted to previously established cyclization conditions (Table 1, entry 1), the pure 14-membered macrocycle **67** was obtained in 66% yield after a simple extraction.[36] The reaction appeared to be a spot to spot transformation, but some material was lost during extraction because of its low solubility in common organic solvents. No higher molecular weight species resulting from dimerization or oligomerization were detected in the mass spectra of the crude reaction product. In searching for even milder reaction conditions, macrocyclization of **66a** to **67** was examined under a range of experimental conditions. Table 1 indicates that CsF was an excellent base to promote the desired intramolecular S_NAr reaction, while Li_2CO_3 and $NaHCO_3$ were ineffective presumably because of their insufficient basicity. Addition of 18-crown-6 (entry 3) dramatically accelerates the reaction presumably due to the increased nucleophilicity of "naked" alkoxide anion.

In view of the ready availability of chlorosubstituted aromatic compounds, macrocyclization using chloride as leaving group appeared as an attractive alternative. No cyclization reaction occurred when **66b** was treated under our standard conditions (entry 6) in agreement with the low "leaving ability" of chloride related to fluoride in S_NAr reactions. At 40°C, cyclization did occur, however the conversion was low. Prolonged stirring at this temperature led to degradation, indicating that either **66b** or the cyclized product **67** was unstable at this temperature. Curiously, the optimized conditions for the cyclization of **66b** required heating to 80°C for a shorter period of time (6h, 80%, entry 9). In view of lower reactivity of chloride and sensitivity of the arylglycine unit towards racemization, fluorine containing substrates were used exclusively in the following studies.

In order to determine the minimal functional units needed for the antibacterial activity, the 14-membered macrocycles **73** was targeted.[37] In this regard, the presence of an aromatic amino group, though less basic than the aliphatic one, may facilitate formation of an initial "loose" complex with carboxylate anion. Secondly, the presence of an amino substituent in the aromatic ring may rigidify the cyclic framework and thus be beneficial to the binding interactions. Finally, this study provided an opportunity to test macrocyclization in the hitherto unknown case where the nitro group is located *para* to the fluoride leaving group.

Table 1. Representative Results of the Macrocyclization Reaction[a]

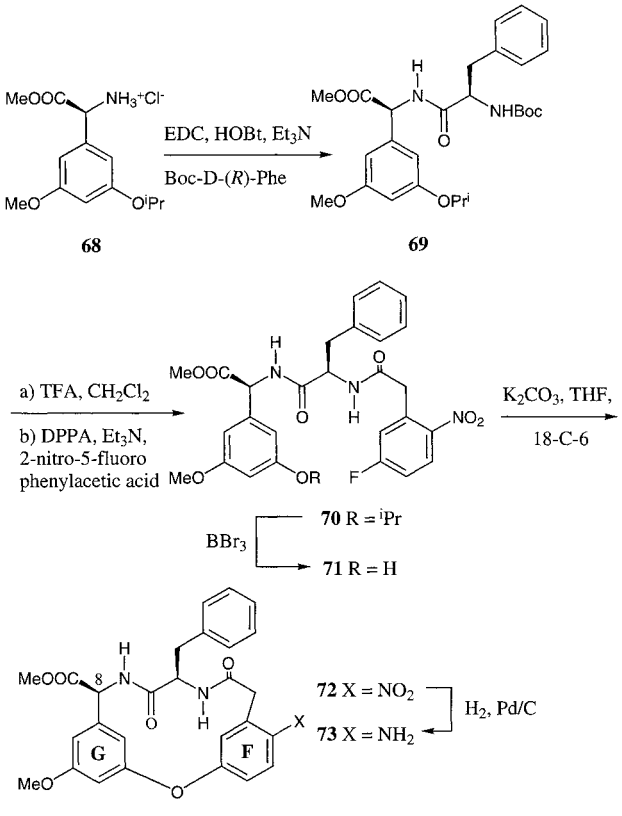


66a: X = F
66b: X = Cl

67

entry	base (eq.)	additive	temperature, time	yield
	X = F			
1	K_2CO_3 (3)	no	r t, 20h	66%
2	CsF (5)	no	r t, 20h	62%
3	K_2CO_3 (3)	18-crown-6	r t, 6h	82%
4	Li_2CO_3 (30)	no	r t, 4 days	no reaction
5	$NaHCO_3$ (3)	no	r t, 2 days	trace
	X = Cl			
6	K_2CO_3 (3)	no	r t, 2 days	no reaction
7	K_2CO_3 (3)	no	40°C, 24h	degradation
8	K_2CO_3 (3)	18-crown-6	r t, 2 days	degradation
9	K_2CO_3 (3)	no	80°C, 6h	80%

[a]All reactions were run in dry DMF at the concentration of 0.01M



68 **69**

Scheme 11

Coupling of methyl 3-methoxy-5-isopropyloxy phenylglycine (**68**), obtained *via* asymmetric Strecker reaction (*cf.* Scheme 7), with Boc-D-Phe (EDC, Et_3N) furnished the dipeptide **69**. Mild acidic deprotection (TFA, CH_2Cl_2) followed by amide bond formation (DPPA, Et_3N) with 5-fluoro-2-nitrophenylacetic acid provided the tripeptide **70** very efficiently. Chemoselective deprotection (BCl_3) afforded the linear tripeptide **71** in 92% yield (Scheme 11).

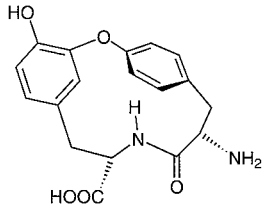
After searching for different reaction parameters, we found that anhydrous THF in the presence of K_2CO_3 and a catalytic amount of 18-crown-6 was optimal. Compound **72**, isolated in 71% yield, had spectral data (^1H and ^{13}C NMR , IR, HRMS) consistent with the proposed macrocyclic structure. Suprisingly, the macrocycle **72** in contrast to its precursor **71** was configurationally stable under mild basic conditions. We reasoned that the extra ring constraints introduced by enolization of the ester function as well as non-coplanarity of C-8 and the aromatic ring **G** may explain the reduced kinetic acidity of H-8 and thus the increased configurational stability. It is worthy noting that teicoplanin was readily epimerized at the α-carbon centre of amino acid **3** under basic conditions.[38]

Hydrogenation (H_2, Pd/C, MeOH-CH_2Cl_2, 1h) of **72** afforded the amino compound **73** in excellent yield. Interestingly, in the ^1H NMR spectrum of **73**, the H-20 signal (δ 6.02 ppm) was shifted upfield compared to that of **72** (δ 6.48 ppm) suggesting that conformational changes had been induced after reduction of the nitro group. The relative position of the two aromatic rings **F** and **G** was modified in such a way that H-20 was now located under the plane of ring **F** in its shielding region. NOE studies show that the conformation of **73** is very similar to that of the compound prepared by Chakraborty.[39]

III-B. Synthesis of cycloisodityrosine

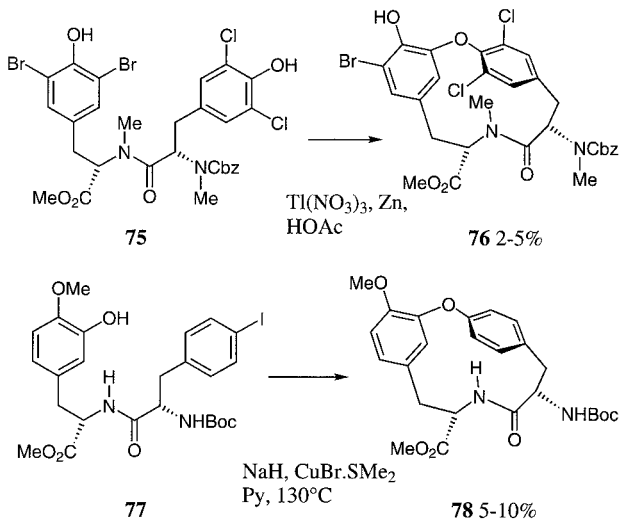
Cycloisodityrosine (**74**) is the key subunit (pharmacophore) of several bioactive natural products, such as piperazinomycin (**3**), bouvardin (**4a**), deoxybouvardin (**4b**) and the structurally related bicyclic hexapeptides RA I-XIV (Figure 1).

Efforts to examine critically the biological role of cycloisodityrosine

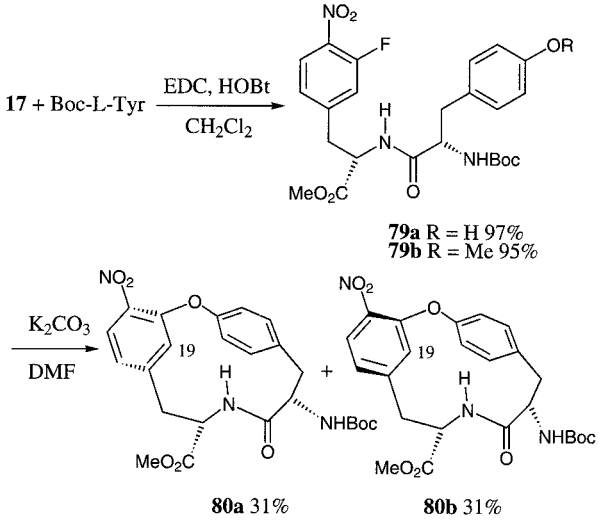


74 cycloisodityrosine

Figure 6

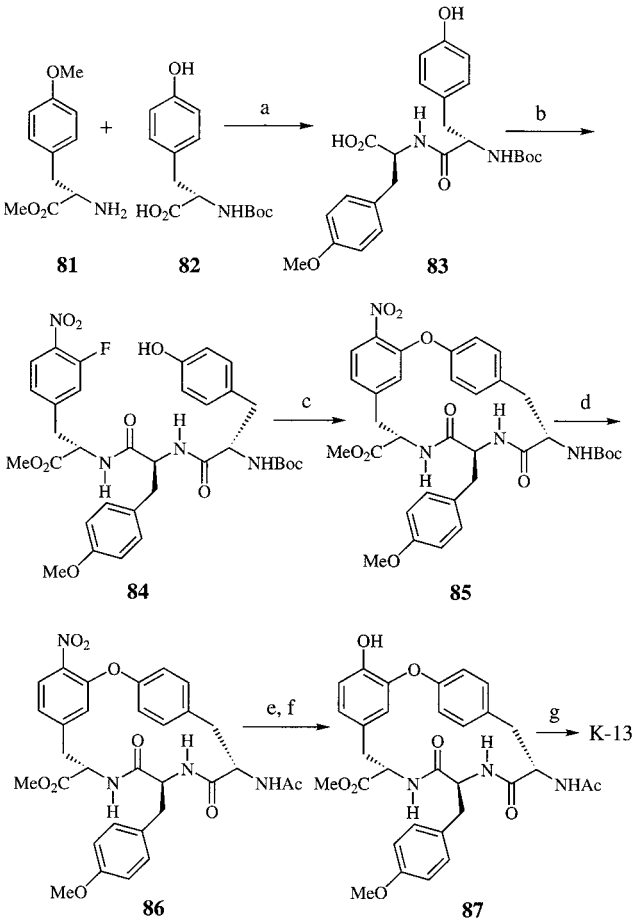


Scheme 12



Scheme 13

derivatives have been limited by their synthetic inaccessibility. This deceptively simple molecule is in fact a challenging synthetic target. Until now, only two groups[9c, 11a] have achieved such syntheses in yields ranging from 2 to 10% (Scheme 12). As shown in Scheme 13, the intramolecular S_NAr reaction provided a simple solution to this prob-



Reagents and Conditions: a) (i) EDC, HOBt, (ii) K_2CO_3, MeOH-H_2O; b) EDC, HOBt, **17a**; c) K_2CO_3, DMF; d) (i) TFA; (ii) $NaHCO_3$, Ac_2O; e) Fe-$FeSO_4$; f) HBF_4, ^tBuONO, MeOH, then $Cu(NO_3)_2$, Cu_2O, H_2O. g) $AlBr_3$, EtSH.

Scheme 14

lem.[40] Coupling of **17a** with N-Boc-L-Tyr (EDC, HOBt) gave the dipeptide **79** (97%) which was cyclized (K_2CO_3, DMF, rt) to afford a 1/1 mixture of atropisomers **80a** and **80b** (62%). Apparently the S_NAr reaction proceeded much faster than the intramolecular N-acylation[11a] which is a major side reaction in Boger's Ullmann based strategy.

Mass spectra and elemental analysis reveal that **80a** and **80b** are constitutional isomers calculated for $C_{24}H_{27}N_3O_8$. In ^1H NMR spectra, both compounds exhibited a characteristic, strongly shielded H-19 signal (5.34 and 5.37 ppm) due to the anisotropic effect of the tyrosine aromatic ring, indicative of a cyclized structure. Attempted thermoatropisomerization in DMSO-d_6 at 110°C failed to give any equilibrium, probably due to the high energy required for this process. A control experiment showed that no interchange of these two cyclic compounds occurred under the above S_NAr conditions and more importantly, that diastereomerically pure **79b** (R = Me) was recovered quantitatively under the same cyclization conditions. These results gave indirect evidence that the two cyclized products did not result from epimerization of two stereogenic centres and therefore they are atropisomers. While this point needs to be proven, it is interesting to note that in two literature syntheses of cycloisodityrosine, different physical data have been reported for the same structure! Moreover, Inoue *et al.*[9c] noted that the 14-membered cycloisodityrosine, obtained *via* oxidative coupling method, is an equilibrium mixture of two compounds. We think that these two *separable* compounds might well be the two atropisomers.

IV. Synthesis of 17-membered macrocycle: A novel synthesis of K-13

The total synthesis of K-13 has been reported by several groups following a common linear synthetic strategy, *i.e.*: Ullmann biaryl ether coupling of two simple aromatic compounds followed by elaboration of the biaryl ether side chain into amino acid and ultimately by macrolactamization. The only exception is the thallium trinitrate promoted two-step sequence, developed by Yamamura *et al.*,[9a] for achieving the intramolecular oxidative phenolic coupling. However, the yield of this cyclization step was lower than 15%. Successful implementation of intramolecular S_NAr reaction in the synthesis of 17-membered macrocycle allowed us to develop a highly convergent synthesis of K-13 (Scheme 14).[41]

The tripeptide **84** prepared by coupling of two L-(*S*)-Tyr units and methyl 3-fluoro-4-nitrophenyl alanate (**17a**) was submitted to our standard macrocyclization conditions (K_2CO_3, DMF, 0.02M, rt, 4hrs) to afford the 17-membered cyclic peptide **85** (87%). Mild acid hydrolysis of the *tert*-butyloxycarbonyl carbamate (Boc) followed by conventional acetylation provided **86** in 83% overall yield. Reduction of the nitro group to amine, diazotization (HBF_4, ^tBuONO, MeOH) and subsequent oxidative hydrolysis of the diazonium salt [$Cu(NO_3)_2 \cdot 3H_2O$ and Cu_2O] afforded the protected K-13 **87** {$[\alpha]_D$ -14 (*c* 0.16, MeOH)} in 74% yield. Demethylation of **16** to natural K-13 (**1**) had already been reported by Evans' group.[42]

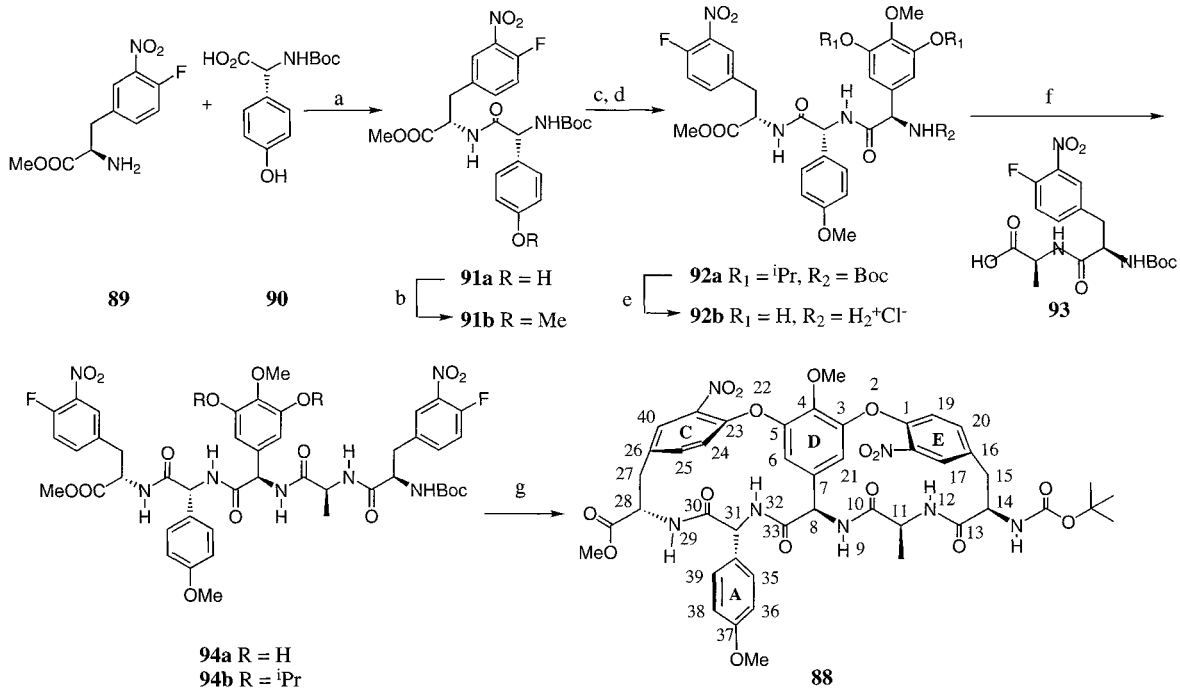
V. Synthesis of bicyclic rings of vancomycin and teicoplanin

Having established the validity of intramolecular S_NAr reaction in the synthesis of 14-, 16- and 17-membered macrocycles, we subsequently applied this method in the synthesis of more advanced **C**-O-**D**-O-**E** ring (16+16) of vancomycin and **D**-O-**E**-**F**-O-**G** ring (16+14) of teicoplanin.

V-A Synthesis of a model bicyclic C-O-D-O-E ring (16+16) of vancomycin

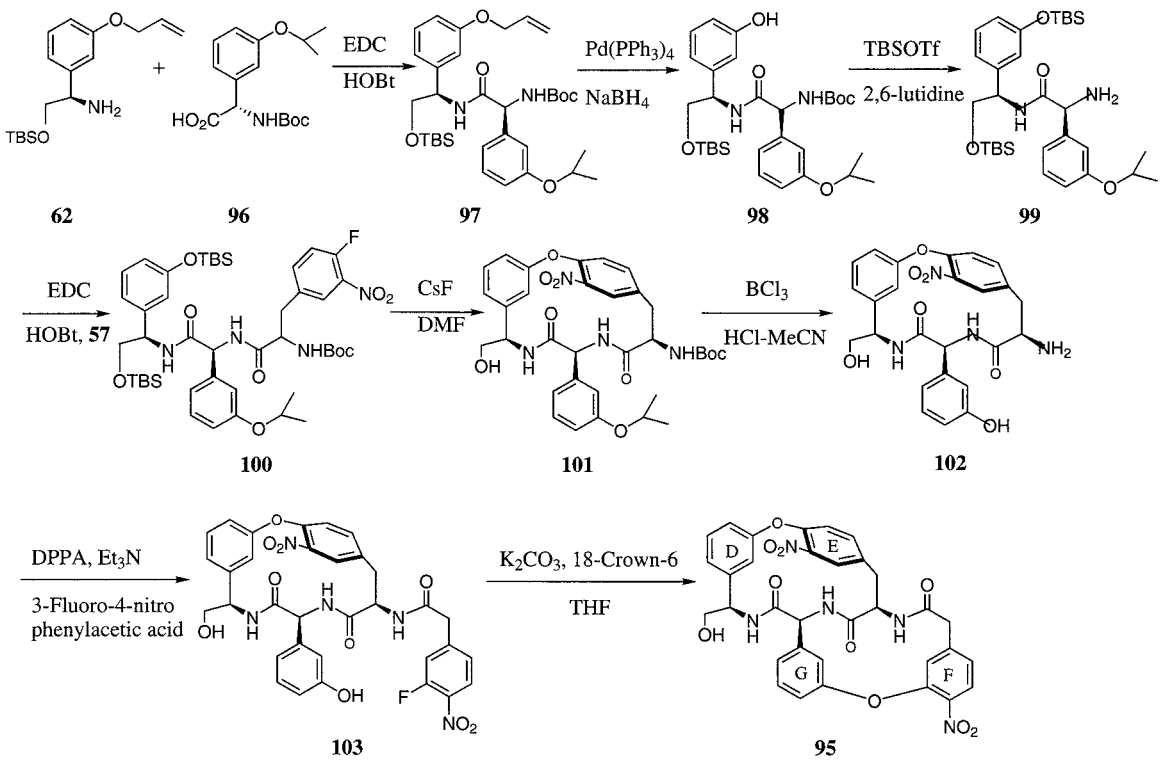
Synthesis of a model bicyclic **C**-O-**D**-O-**E** ring (16+16) of vancomycin **88**[43] *via* one-pot, double intramolecular S_NAr reaction is described in Scheme 15. [3 + 2] Segment coupling between the tripeptide **92b** and the dipeptide **93** gave the pentapeptide **94a** (65%). This reaction is noteworthy since the two phenolic functions did not need to be protected and no trace of O-acylated compound was isolated.

Cyclization of **94a** was first attempted at room temperature, by means of different bases (K_2CO_3, CsF) in different solvents (DMF, DMSO) with or without additive (18-crown-6). In every case, the reaction mixtures contained at least four cyclized compounds and this result was tentatively attributed to the presence of two newly created axial chiral centres. When the cyclization was performed at -5°C using dry CsF as promoter in DMF (0.01 M), one major product **88** was isolated in 60% yield whose cyclized structure was evidenced by the presence of characteristic upfield shielded protons H-6 and H-21.[44]



Reagents and Conditions: a) EDC, HOBt, CH_2Cl_2, 92%; b) CsF, MeI, DMF, 83%; c) TFA-CH_2Cl_2, anisole; d) EDC, HOBt, CH_2Cl_2, Et_3N, N-Boc D-3,5-diisopropyloxy-4-methoxy phenyl glycine; e) BCl_3, CH_2Cl_2, then MeOH, 100%; f) EDC, HOBt, Et_3N, CH_2Cl_2, 65%; g) CsF, DMF, -5°C, 60%.

Scheme 15



Scheme 16

To verify if any racemization had occurred during the cyclization, the pentapeptide **94b**, where two phenol functions were protected, was prepared from **92a** following the same synthetic scheme. When **94b** was submitted to the above mentioned cyclization conditions for 4 days, it was recovered quantitatively without epimerization. This control experiment clearly show that little, if any, racemization had occured under the cyclization conditions. The assignment of ^{1}H NMR spectra of **88** was based on COSY, NOESY experiments performed in CD_3CN and in DMSO-d_6 solution at 60°C. The stereochemistry of the amide bonds (all *trans* configurations) and that of two axial chiral centres were established by NOE studies to be as shown in scheme 15. Representative NOE cross peaks of **88** were as follows: NH32/H35, H6, H8; NH29/H31; H17/H15; H40/H27', NH9/H21, Me; H25/H28, H27; H20/H15'; H19/H21; H24/H6, H14/H20. The NOEs between H25/H28 and H14/H20 are diagnostic for the assignment of atropstereocentre. We are currently determining the stereochemistry of the other atropisomers and attempting to steer the cyclization towards formation of the desired atropisomer.

V-B. Synthesis of a model bicyclic D-O-E-F-O-G ring of teicoplanin

The synthesis of **D**-O-**E**-**F**-O-**G** ring of teicoplanin **95**[45] is depicted in Scheme 16. Reductive removal of the allyl protecting group of **97** [$Pd(PPh_3)_4$, $NaBH_4$][31] afforded compound **98** (85%) with less than 5% racemization. TBDMSOTf mediated removal of Boc protecting group provided the amine **99**, which was coupled with D-(*R*)-Boc-4-fluoro-3-nitrophenylalanine **57** to furnish the tripeptide **100** in excellent yield. The tiny amount of the undesired diastereoisomer was readily removed by flash chromatography.

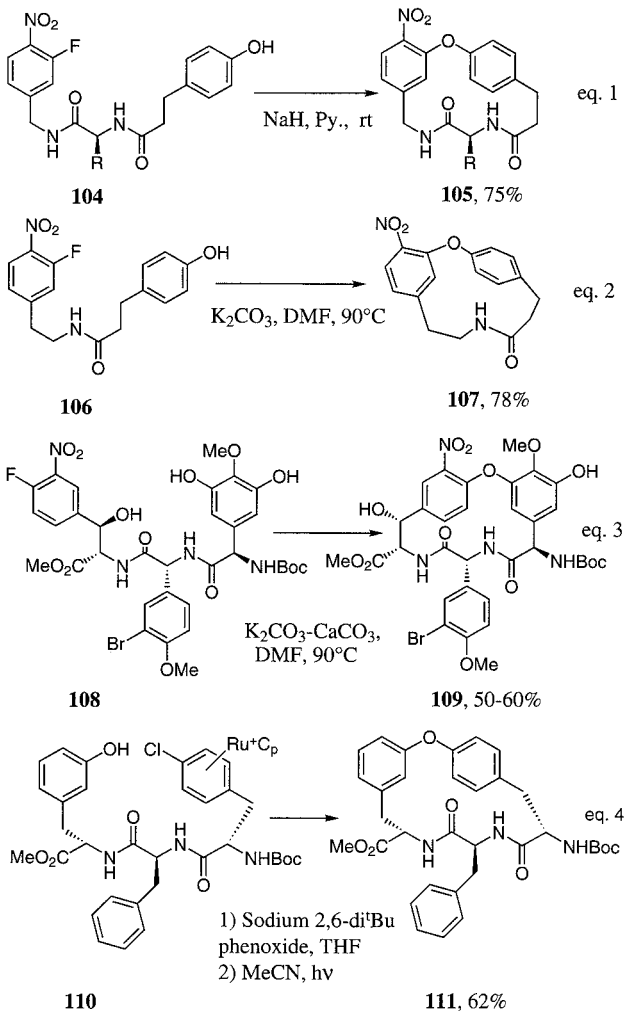
Macrocyclization of diastereomerically pure **100** (dry CsF, DMF, 0.01M) gave the desired macrocyclic **D**-O-**E** ring **101** (84%) as a single atropisomer whose stereochemistry was determined from NOE studies (*vide supra*). To ascertain the absence of racemization in this key ring closure step, racemic amino acid (±)-**96** was prepared *via* Strecker synthesis and incorporated into the tripeptide **100** following the same synthetic sequence. Flash chromatography separation gave then the diastereomerically pure compounds **100** (*R*, *S*, *R*) and *epi*-**100** (*R*, *R*, *R*). Cyclization of the latter under conditions identical to those used for **101** afforded the macrocycle *epi*-**101** which was clearly different in its TLC and spectral properties from **101**. This result convincely proved that no racemization had occured under our macrocyclization conditions. It is interesting to note that CsF plays a dual role in this cyclization reaction: it deprotects TBS ethers and promotes the cyclization in a one-pot fashion.

The synthesis of the bicyclic **D**-O-**E**-**F**-O-**G** ring model **95** was completed as follows. Deprotection of **101** (BCl_3) led to amino compound **102** (73%) which was coupled with 3-fluoro-4-nitrophenylacetic acid (DPPA) to provide the desired macrocyclization precursor **103** (65%). The optimized conditions for cyclization of **103** were found to be 10 eq. of K_2CO_3 in THF in the presence of 18-crown-6. Under these conditions, the bicyclic **D**-O-**E**-**F**-O-**G** ring **95** was isolated in 87% yield. Given that this bicyclic system is obviously strained, the high yield obtained under mild conditions in the second macrocyclization step is remarkable.

The sequential macrocyclization reported in this synthesis allows differentiation of the two nitro groups and consequently introduction of different functionalities (Cl in ring **E**, OH in **F**) found in teicoplanin. The bicyclic **D**-O-**E**-**F**-O-**G** ring model **95**, obtained in 19% overall yield from **62**, is the most advanced synthetic intermediate to date on the way to the total synthesis of teicoplanin and related antibiotics.

VI. Conclusion

We have demonstrated that the use of intramolecular S_NAr reaction opens ample opportunities for the total synthesis of biologically active compounds. The development of this new synthetic strategy was of course motivated by the synthetic challenge of complex natural products, examplified by vancomycin. To date, the wealth of experimental evidences and theoretical interpretations related to cyclizations has led to a considerable understanding of intramolecular reactivity. Yet, the exact source of rate enhancement is still a matter of controversy. In the case studied, we think that the *intramolecular recognition phenomenon* leading to the preorganized cyclization precursor may be the main source of the successful implementation of our above discussed intramolecular S_NAr strategy. The concept of *intermolecular recognition phenomenon* has been very fruitful in supramolecular chemistry[46] as well as in evaluation of chiral selectors,[47] we may anticipate that the *intramolecular recognition phenomenon* could also provide a useful guide in designing a novel macrocyclization technique.



Scheme 17

While most of the self-imposed constraints discussed at the beginning of this account have been fulfilled by the implementation of intramolecular S_NAr reaction, factors controlling atropdiastereoselectivity in the ring forming step, one of the most challenging issues in terms of the total synthesis of vancomycin still needs to be defined. Studies towards this end and further applications of this methodology in natural product synthesis should be interesting and fruitful.

Shortly after our initial report, other groups, notably Rama Rao's (eq. 1),[48] Boger's (eq. 2 and 3)[49], Rich's (eq. 4)[50] and very recently Evans'[51] have adopted the intramolecular S_NAr based strategy (Scheme 17) and thus witnessed its power in natural product synthesis.

The efficient synthesis of bicyclic **C**-O-**D**-O-**E** ring together with Evans' brilliant synthesis of the 12-membered macrocycle **A**-**B** fragment[52] of vancomycin open the way to a long awaited total synthesis of vancomycin.

Acknowledgement: I am profoundly indebted to Dr. Beugelmans whose illuminating and stimulating discussion have made this research possible. I wish to express my sincerest gratitude to all coworkers whose names are given in the references. Their enthusiasm and diligence have been instrumental in the development of the chemistry described in this account. Generous financial support from CNRS is gratefully acknowledged.

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